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Symposium on Disturbances of nutrient homeostasis in diabetes

Abnormalities of glucose homeostasis in diabetes

BY MALCOLM NATTRASS

General Hospital, Steelhouse Lane, Birmingham B4 6NH

The World Health Organization classification of diabetes mellitus recognizes two major types of diabetes in the Western world (World Health Organization, 1985). Insulin-dependent (type 1) and non-insulin-dependent (type 2) are justifiably separate entities differing in aetiology, pathogenesis, and to some extent biochemical and clinical manifestation.

In the aetiology of type 1 diabetes three components are acknowledged. In addition to the interaction of a genetic background with an environmental trigger there is also an immunological factor. The particular genetic background predisposing to type 1 diabetes lies in the individual possessing human leukocyte antigens DR3 or DR4, or both, with attempts being made to identify the sub-set of the DR region more specific in its susceptibility. The environmental trigger remains elusive, although it is clear that certain viruses, particularly the mumps and rubella viruses, may be instrumental. Newly diagnosed insulin-dependent diabetics also have circulating antibodies to cells of the islets of Langerhans. It is postulated that damage to the islets from the environmental trigger on a particular genetic background initiates or allows further damage from these antibodies leading to islet destruction. Thus, the pathogenesis of type 1 diabetes is islet destruction and insulin deficiency.

The actions of insulin are well recognized and the metabolic abnormality of type 1 diabetes entirely predictable. Hyperglycaemia is the result of unrestrained hepatic glucose output and impaired peripheral glucose utilization. The former is a consequence of increased gluconeogenesis, increased glycogen breakdown, and impaired glycogen storage. Decreased peripheral utilization is mainly a consequence of impaired uptake of glucose by the metabolically active tissues muscle and fat. Fat metabolism is also profoundly affected by insulin deficiency. With reduced glucose uptake into the fat cell there is a shortage of α-glycerophosphate for re-esterification of non-esterified fatty acid. More importantly in severe insulin deficiency lipolysis is enhanced. Thus, release of non-esterified fatty acids is enhanced providing substrate for hepatic ketogenesis. Less well documented is the impairment of peripheral utilization of ketone bodies resulting from insulin deficiency. Hyperglycaemia and hyperketonaemia are the major metabolic consequences of insulin deficiency which in the extreme are seen in the patient in the

clinical presentation of diabetic ketoacidosis. Even in this condition, however, a pure defect of insulin deficiency is rarely seen (Schade *et al.* 1981). To the effect of insulin deficiency must be added the opposing effects to insulin of increased secretion of catabolic hormones. These hormones, particularly catecholamines and glucagon, but also cortisol and growth hormone exacerbate the hyperglycaemia and hyperketonaemia.

It might be thought that correction of the metabolic consequences of insulin deficiency is a simple matter of giving insulin. Unfortunately there is an immense gulf between giving insulin and ensuring physiological insulin replacement, the true goal of treatment. A brief glance at normal physiology illustrates this challenge. In normal people insulin is secreted promptly into the portal vein in response to meals and snacks. Thus, even the best-disciplined normal subject who restricts their eating to three major meals daily will have peaks of circulating insulin secreted promptly in response to meals superimposed on a low background secretion of insulin in the post-absorptive state. Those normal subjects who snack their way through the day will produce many more peaks of insulin secretion. The difficulties with insulin replacement begin at the first hurdle. Except in unusual circumstances insulin is not given into the portal circulation but is given peripherally. Thus, the portal:peripheral concentration ratio is 1:1 in the diabetic compared with 2:1 in the normal subject. The result in the diabetic is that either the liver is under-insulinized or the periphery over-insulinized. Neither do current insulin preparations allow a prompt rise in circulating insulin after injection. Even quick-acting insulins require >30 min to achieve adequate circulating levels which then persist for 2–6 h. Thus, the peak of insulin secretion in the normal subject becomes a broader based plateau in the insulin-dependent diabetic. Finally there is the problem of tailoring an insulin regimen to the patient's eating habits. It is clear that one or two injections daily cannot begin to mimic normal physiology unless the patient has abnormal eating habits. Yet it is a major step for the physician to recommend, and the patient to accept, a regimen of three or four injections daily. Such a regimen would have been difficult to accept with the traditional cumbersome insulin syringes and technique, but fortunately is more acceptable with pen-injection devices (Walters *et al.* 1985). Even with more frequent injections the limits set by insulin preparations and peripheral injection render obtaining and maintaining physiological euglycaemia an unattainable goal in most insulin-dependent diabetics. Thus, the majority of the insulin-dependent diabetic patients will display some metabolic abnormalities for part of each day. These are a consequence of under- and over-insulinization. Under-insulinization typically occurs overnight and fasting blood will show hyperglycaemia of varying degree and an element of hyperketonaemia. Following food and insulin, blood glucose and ketone bodies fall rapidly and blood lactate may show a marked rise. Adequate insulin replacement to obtain euglycaemia inevitably results in over-insulinization of the periphery with suppressed concentrations of non-esterified fatty acids, glycerol, and total ketone bodies. It is this thin line between under- and over-insulinization which remains the major challenge to both physician and patient in the treatment of insulin-dependent diabetes.

The aetiology of non-insulin-dependent diabetes is less clear. While acknowledging that there is a strong genetic predisposition the nature of this is unknown; nor is the environmental stimulus identified with certainty, with only obesity a likely candidate in some (West, 1978), but by no means all, patients. This absence of knowledge presents difficulties in identification of a homogeneous group of patients and, indeed, the disease may well be a heterogeneous collection. For studies of pathogenesis, therefore, most

investigators have chosen to study a homogeneous group by selecting obese non-insulin-dependent diabetics. Since obesity *per se* has profound effects on metabolism this may not be ideal, and certainly there are difficulties in interpretation.

The fundamental question in the pathogenesis of non-insulin-dependent diabetes is whether it is a disease of insulin secretion or insulin resistance. The advent of radioimmunoassay for insulin produced measurements of insulin concentration, particularly in obesity, which were clearly supranormal, both fasting and after an oral glucose stimulus (Yalow & Berson, 1960). Further work in obese non-insulin-dependent diabetics demonstrates that these patients have higher insulin concentrations than lean non-diabetic subjects but lower insulin concentrations than obese non-diabetics. Interpretation of this finding is difficult because of differing glucose concentrations between groups, but it is logical to conclude that if insulin concentrations in the obese diabetics are higher than lean normals, yet there is hyperglycaemia, there must be an element of insulin resistance. Comparison with the obese non-diabetics allows a second conclusion that if glucose concentrations are higher in the diabetics but insulin is lower then there must also be an element of undersecretion of insulin.

Recent years has seen an explosion of interest in insulin resistance, although such a concept has been identified since the 1930s. Himsworth & Kerr (1942) divided diabetics into insulin sensitive and insulin resistant on the basis of the blood glucose response to simultaneous administration of glucose and insulin. They identified the characteristics of the insulin-sensitive group as younger age of onset and thinner than the insulin-resistant group, indicating an essential difference between two types of diabetes which would equate to more modern concepts of insulin-dependent and non-insulin-dependent diabetes. Reaven and his group (Ginsberg *et al.* 1975) took up this challenge with a quadruple-infusion technique of glucose, insulin and adrenaline, to inhibit endogenous insulin secretion, and propanolol to block beta effects of adrenaline. They argued that for similar infusions of glucose and insulin, and a similar level of circulating insulin any differences in steady-state glucose levels were a measure of the ability of a patient or a group of patients to dispose of glucose in the periphery. Obese subjects and non-insulin-dependent diabetics had higher blood glucose levels than controls and, therefore, the inability to dispose of glucose was a measure of insulin resistance. The introduction of the glucose clamp technique (DeFronzo, 1988) was a major development in the area and has contributed significantly. In this technique euglycaemia is maintained by a variable-rate glucose infusion during infusions of insulin designed to produce predetermined circulating insulin levels. By modifying the insulin infusion, levels of 100, 1000 and even 10 000 mU/l may be obtained, yet euglycaemia preserved. Provided the circulating insulin concentration is sufficient to suppress completely hepatic glucose output then the amount of glucose infused to maintain euglycaemia must be equal to the quantity which is being disposed of in the periphery. Less glucose to maintain euglycaemia means less peripheral disposal and, hence, insulin resistance. In practice because of doubts about suppression of hepatic glucose output in insulin-resistant states most workers now also measure isotopically determined glucose turnover with calculation of hepatic glucose output and peripheral glucose disposal. The unanimous conclusion is that these processes display resistance to insulin in non-insulin-dependent diabetic patients (DeFronzo, 1988).

Less clear is the level at which insulin resistance exists in this condition. Insulin exerts its metabolic effects by first binding to a specific receptor on cell membranes. Insulin

resistance may occur pre-binding, at the binding stage, or during amplification and expression of the signal post-binding.

Of major interest in the pre-binding causes of insulin resistance is the role of metabolites, and hormones. Certain intermediary metabolites, when present in higher than normal concentrations, significantly reduce the effectiveness of insulin action. These include hydrogen ion, ketone bodies and non-esterified fatty acids whose effect is probably the best documented. The glucose–fatty acid cycle of Randle *et al.* (1963) was a demonstration that high concentrations of non-esterified fatty acids reduce glucose uptake into muscle, whereas reducing the level of fatty acids allows an increase in glucose uptake. Thus, for example, during fasting this mechanism allows conservation of the precious resource, glucose. Since elevated non-esterified fatty acids and ketone bodies are a consequence of insulin deficiency or insulin resistance in diabetes, could this be the mechanism of insulin resistance in diabetes? A number of groups have examined this hypothesis recently, with the almost unanimous conclusion that the glucose–fatty acid cycle is not the mechanism (Capaldo *et al.* 1988), although it is difficult to design appropriate experiments which will give a clear answer to the question.

The second major cause of insulin resistance pre-binding is the catabolic or counter-regulatory hormones. Their opposing actions to insulin, particularly marked with the catecholamines, glucagon, cortisol, and growth hormone, are well documented. Diabetes or impaired glucose tolerance is a feature of diseases where these hormones are secreted in excess, such as acromegaly or Cushing's syndrome.

Clinically the effect of pre-binding causes of insulin resistance is small. In diabetic ketoacidosis, for example, where at presentation levels of non-esterified fatty acids, ketone bodies, hydrogen ion and catabolic hormones are markedly raised, insulin resistance is present to a minor degree.

Changes in the insulin receptor can result in insulin resistance either through a change in binding affinity or through a reduction in the number of insulin receptors. In practice it is unclear whether a pure binding defect is ever the only abnormality which results in insulin resistance, although some studies have suggested this may be so in patients with impaired glucose tolerance.

More important are defects post-binding. The full picture of insulin's second messenger defies elucidation, but significant progress has been made in recent years and it is now recognized that the first event after binding is phosphorylation of the insulin receptor. How many steps exist after this, leading to, for example, glycogen synthase (*EC* 2.4.1.21) activation, and which can or does go wrong is not clear, but post-binding abnormalities do occur in both the major clinically insulin-resistant states, obesity and non-insulin-dependent diabetes.

Kahn (1978) introduced an important concept in the study of insulin resistance. He argued that there were two components of insulin resistance which were labelled insulin insensitivity and insulin unresponsiveness. When considering the dose–response relationship of insulin and a biological action of insulin there are two mechanisms of impairment. First it might be possible to achieve a maximum biological action of insulin with greater than normal insulin concentrations, and second it might be impossible to obtain a maximum biological action. The former, or a right shift in the dose–response curve is termed insulin insensitivity and the latter unresponsiveness. Insulin insensitivity was equated with a reduction in insulin receptor number, while unresponsiveness was determined by a post-receptor defect. In other words, if the post-receptor mechanism is

intact, recruitment of sufficient binding sites will eventually overcome the defect in insulin receptor number. If the post-binding pathway is defective, then no matter how high the insulin concentration this will persist and ameliorate the response.

These defects can be shown in non-insulin-dependent diabetes, although interestingly there are differences between metabolic processes. Thus, peripheral glucose uptake displays insulin unresponsiveness during a euglycaemic clamp, even with insulin concentrations >1000 mU/l failing to produce a normal maximal biological response. In contrast, inhibition of hepatic glucose output displays the characteristics of insulin insensitivity.

This still leaves us a considerable way from the pathogenesis of non-insulin-dependent diabetes. Does an element of insulin deficiency lead to tissues which are resistant to the actions of insulin, or is it that insulin resistance places demands on the pancreas to increase its output of insulin, and when this demand cannot be met non-insulin-dependent diabetes develops? These questions are, as yet, unanswered.

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